PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 413/04, 417/04, A61K 31/535 — A1

(11) International Publication Number: **WO 97/18206**

(43) International Publication Date: 22 May 1997 (22.05.97)

(21) International Application Number: PCT/GB96/02766

(22) International Filing Date: 13 November 1996 (13.11.96)

(30) Priority Data:
9523244.3 14 November 1995 (14.11.95) GB

(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SWAIN, Christopher, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). TEALL, Martin, Richard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). WILLIAMS, Brian, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

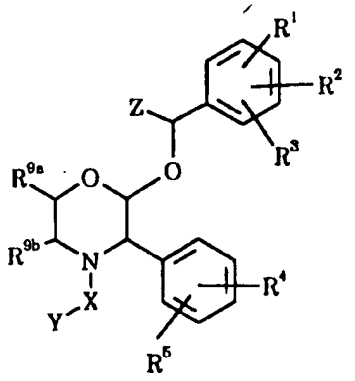
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

The present invention relates to compounds of formula (I) wherein X is a 5- or 6-membered C-linked heteroaromatic ring containing 1 to 4 nitrogen atoms and optionally containing in the ring one oxygen or sulphur atom; Y is a group of the formula $-(CH_2)_nNR^6R^7$, or a methylene- or ethylene-linked imidazolyl group; Z is hydrogen or C_{1-4}alkyl optionally substituted by a hydroxy group; R^1, R^2, R^3, R^4, R^5, R^{9a} and R^{9b} are a variety of substituents; R^6 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxy; R^7 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxy or a 4-, 5- or 6-membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S; or R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring or a non-aromatic azabicyclic ring system; and n is zero, 1 or 2; or a pharmaceutically acceptable salt thereof. The compounds are of particular use in the treatment or prevention of pain, inflammation, migraine, emesis and postherapeutic neuralgia.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of morpholine derivatives which are useful as tachykinin antagonists.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-NH_2

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the NK_1, NK_2 and NK_3 receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

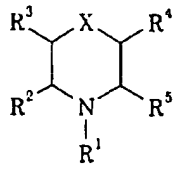
For instance, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, *Ciba Foundation Symposium* 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem*, (1982) 25, 1009) and in arthritis [Levine *et al* in *Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al* in *Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al*, *Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al*, *Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al*, *Science* (1988) 241, 1218-21 and Kimball *et al*, *J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al*, *Proc. Natl. Acad. Sci., USA* (1988) 85, 3235-9] and, possibly by arresting or slowing ß-amyloid-mediated neurodegenerative changes [Yankner *et al*, *Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al*, *Cancer Research* (1992) 52, 4554-7].

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*The Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

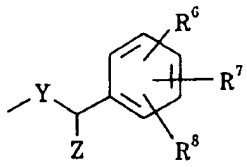
European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



wherein R^1 is a large variety of substituents;

R^2 and R^3 are *inter alia* hydrogen;

R^4 is *inter alia*



;

R^5 is *inter alia* optionally substituted phenyl;

R^6, R^7 and R^8 are a variety of substituents;

X is O, S, SO or SO_2;

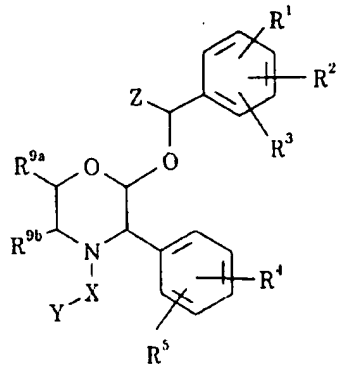
Y is *inter alia* O; and

Z is hydrogen or C_{1-4}alkyl.

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

It is desirable that compounds may be administered orally and by injection. Certain compounds have now been discovered which act as potent non-peptide tachykinin antagonists and which, by virtue of their advantageous aqueous solubility, are particularly easily formulated for administration by both the oral and injection routes, for example in aqueous media.

The present invention provides compounds of the formula (I):



(I)

wherein

X is a 5- or 6-membered C-linked heteroaromatic ring containing 1 to 4 nitrogen atoms and optionally containing in the ring one oxygen or sulphur atom;

Y is a group of the formula $-(CH_2)_nNR^6R^7$, or a methylene- or ethylene-linked imidazolyl group;

Z is hydrogen or C_{1-4}alkyl optionally substituted by a hydroxy group;

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^3 is hydrogen, halogen or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxy;

R^7 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxy or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring of 4 to 7 ring atoms, which ring may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR^8, S(O) or $S(O)_2$ and which ring

may be optionally substituted by one or two groups selected from hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, oxo, COR^a or CO_2R^a where R^a is as previously defined;

or R^6 and R^7 together with the nitrogen atom to which they are attached, form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

R^8 is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring; and

n is zero, 1 or 2;

and pharmaceutically acceptable salts thereof.

A preferred class of compounds of formula (I) is that wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Another preferred class of compounds of formula (I) is that wherein R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Also preferred is the class of compounds of formula (I) wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

A particularly preferred class of compounds of formula (I) is that wherein R^1 is fluorine, chlorine or CF_3.

Another particularly preferred class of compounds of formula (I) is that wherein R^2 is hydrogen, fluorine, chlorine or CF_3.

Also particularly preferred is the class of compounds of formula (I) wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^1 and R^2 are in the 3 and 5 positions of the phenyl ring.

More preferably R^1 is 3-fluoro or 3-CF_3.

More preferably R^2 is 5-fluoro or 5-CF_3.

More preferably R^3 is hydrogen.

Most preferably R^1 is 3-F or 3-CF_3, R^2 is 5-CF_3 and R^3 is hydrogen.

A further preferred class of compound of formula (I) is that wherein R^4 is hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

Yet another preferred class of compounds of formula (I) is that wherein R^6 represents hydrogen, C_{1-6}alkyl or C_{2-4}alkyl substituted by C_{1-6}alkoxy.

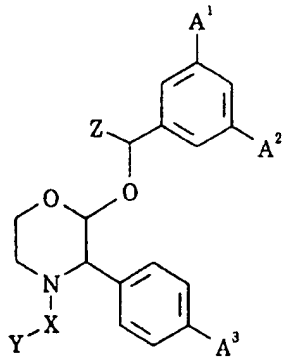
A yet further preferred class of compounds of formula (I) is that wherein R^7 represents hydrogen, C_{1-6}alkyl or C_{2-4}alkyl substituted by C_{1-6}alkoxy.

Also preferred is the class of compounds of formula (I) wherein R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring of 4, 5 or 6 ring atoms which may optionally contain in the ring one oxygen atom or the group NR^8 (where R^8 is hydrogen or methyl) and which ring may be optionally substituted by hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, oxo, COR^a or CO_2R^a.

In particular, the group NR^6R^7 preferably represents NH_2, $NHCH_3$, $N(CH_3)_2$, azetidinyl, morpholino, thiomorpholino, piperazino, piperidino or pyrrolidino.

Also preferred is the class of compounds of formula (I) wherein R^{9a} and R^{9b} are each independently hydrogen or methyl. Preferably R^{9a} is hydrogen. Preferably R^{9b} is hydrogen. Most preferably R^{9a} and R^{9b} are both hydrogen.

From the foregoing it will be appreciated that a particularly apt sub-group of compounds of this invention are those of the formula (Ia) and pharmaceutically acceptable salts thereof:



(Ia)

wherein

A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

and X, Y and Z are as defined in relation to formula (I).

A preferred group X for compounds of formula (I) or (Ia) is a 5-membered C-linked heteroaromatic ring containing 1 to 4 nitrogen atoms and optionally containing in the ring one oxygen or sulphur atom. Suitable groups include imidazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, thiadiazolyl and oxadiazolyl groups.

A particularly preferred group X for compounds of formula (I) or (Ia) is a 5-membered C-linked heteroaromatic ring containing 2 to 4 nitrogen atoms and optionally containing in the ring one sulphur atom.

An especially preferred class of compound of formula (I) or (Ia) is that where X is an imidazol-2-yl, 1,2,4-triazol-3-yl, thiazolyl-2-yl or tetrazolyl group.

Another preferred class of compound of the present invention is that wherein Y is a group of the formula $-(CH_2)_nNR^6R^7$.

A preferred group Z for compounds of the formulae (I) or (Ia) is a C_{1-2}alkyl group optionally substituted by a hydroxy group, in particular a methyl or CH_2OH group, espeically a methyl group.

Where the group NR^6R^7 forms a saturated heterocylic ring of 4 to 7 ring atoms which may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR^8, S(O) or $S(O)_2$, suitable heterocylic groups include azetidinyl, pyrrolidino, piperidino, homopiperidino, piperazino, N-methylpiperazino, morpholino and thiomorpholino.

Suitable substituents on the saturated heterocyclic ring include CH_2OH, CH_2OCH_3, oxo, CHO, CO_2H, CO_2CH_3, and $CO_2CH_2CH_3$.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogen are fluorine and chlorine of which fluorine is preferred.

When used herein the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The term "alkenyl" as a group or part of a group means that the group is straight or branched and contains at least one double bond. Examples of suitable alkenyl groups include vinyl and allyl.

The term "alkynyl" as a group or part of a group means that the group is straight or branched and contains at least one triple bond. An example of a suitable alkynyl group is propargyl.

Suitable cycloalkyl and cycloalkyl-alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl and cyclobutylmethyl.

Where the group NR^6R^7 represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring is partially saturated, a particularly preferred group is 3-pyrroline.

Where the group NR^6R^7 represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl,

2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.3.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R^7 represents a C_{2-4}alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Specific compounds within the scope of the present invention include:

4-(5-amino-1,2,4-triazol-3-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-N,N-dimethylaminoethyl-2H-tetrazol-5-yl)-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-dimethylaminomethyl)thiazol-2-yl)-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(2-amino-5-thiazolyl)-3-(S)-(4-fluorophenyl)morpholine;

and pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts such as those formed with hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl,

alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The pharmaceutically acceptable salts of the present invention may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

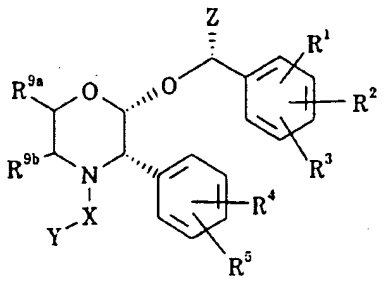
A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as

diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I), and (Ia) will have the 2- and 3- substituent cis and the preferred stereochemistry at the 2-position is that possessed by the compound of Example 1 (i.e. 2-(R)-), the preferred stereochemistry of the 3-position is that possessed by the compound of Example 1 (i.e. 3-(S)), and the preferred stereochemistry of the carbon to which the group Z is attached is either (R) when Z is C_{1-4}alkyl (e.g. methyl) or (S) when Z is C_{1-4}alkyl substituted by hydroxy (e.g. CH_2OH). Thus for example as shown in formula (Ib)



(Ib)

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other

pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in

association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example gylcerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0μm, particularly 0.1 and 0.5μm, and have a pH in the range of 5.0 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably

sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type,

vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, dental pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological

pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or

anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic)

agents, including those routinely used in cancer chemotherapy, and emesis induced by other pharmacological agents, for example, rolipram.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT_3 antagonist, such as

ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or $GABA_B$ receptor agonists such as baclofen. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, triamcinolone, triamcinolone acetonide, flunisolide, budesonide, or others such as those disclosed in US patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. Dexamethasone (Decadron™) is particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis, headache and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D_4 antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction

with other anti-migraine agents, such as ergotamines or 5-HT_1 agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an antiinflammatory agent such as a bradykinin receptor antagonist.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

Suitable classes of anti-anxiety agent include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

Suitable 5-HT_{1A} receptor agonists or antagonists include, in particular, the 5-HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsaperone, and pharmaceutically acceptable salts thereof.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an anti-depressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an anti-depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in

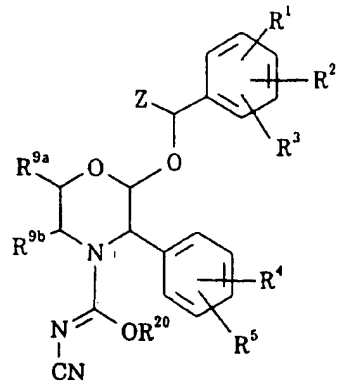
particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to one general process (A), the compounds of formula (I), where X is a 1,2,4-triazol-3-yl group, may be prepared from compounds of formula (II)

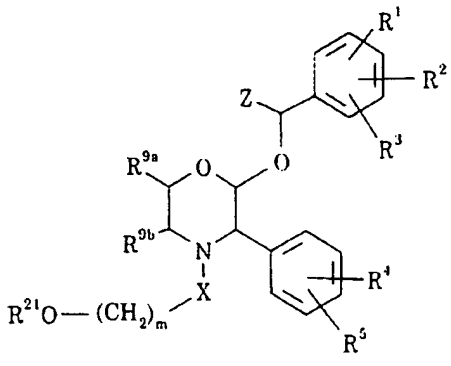


(II)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b} and Z are as defined in relation to formula (I) and R^{20} is phenyl or C_{1-6}alkyl, by reaction with hydrazine.

This reaction may be performed in a conventional manner, for example in a solvent such as an alcohol, for example, 2-propanol, at an elevated temperature between 50°C and 100°C, for example, at about 80°C.

According to another process (B), the compounds of formula (I) may be prepared from compounds of formula (III)



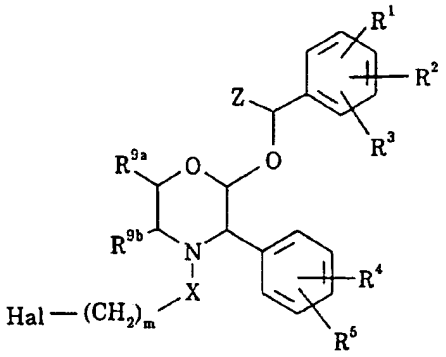
(III)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, X and Z are as defined in relation to formula (I) and R^{21} is a leaving group such as an alkyl- or

aryl-sulphonyloxy group (e.g. mesylate or tosylate), and m is 1 or 2, by reaction with an amine of the formula HNR^6R^7 or imidazole (preferably in the form of its sodium salt).

The reaction is conveniently effected in a suitable organic solvent such as, for example, N,N-dimethylformamide, preferably at elevated temperature and pressure, for example, at 60°C in a sealed vessel.

According to another process (C) the compounds of formula (I) may be prepared from compounds of formula (IV)



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, X and Z are as defined in relation to formula (I) and Hal is a halogen atom such as chlorine, bromine or iodine, especially chlorine, and m is 1 or 2, by reaction with an amine of the formula HNR^6R^7 or imidazole.

The reaction is conveniently effected in a suitable organic solvent such as an alcohol, for example, ethanol, preferably at ambient temperature.

According to another process (D), compounds of formula (I) may be prepared by the interconversion of a compound of formula (I) in which the heteroaromatic ring represented by X is substituted by a group of the formula $-(CH_2)_nNH_2$, by reaction with alkyl halides of the formula R^6-Hal and R^7-Hal, or a suitable dihalide designed to form a saturated

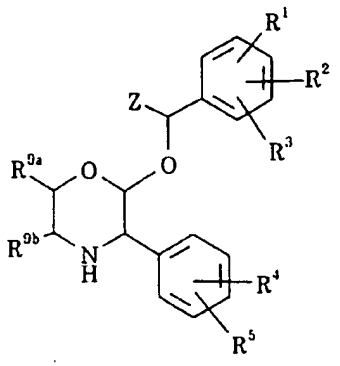
heterocyclic ring, wherein R^6 and R^7 are as previously defined, and Hal is as previously defined, in the presence of a base.

Suitable bases of use in the reaction include alkali metal carbonates, such as, for example, potassium carbonate.

The reaction is conveniently effected in a suitable organic solvent, such as, for example, N,N-dimethylformamide, conveniently at a temperature between room temperature and 80°C, preferably at about 60°C.

Suitable dihalides for forming a saturated heterocyclic ring include, for example, Hal-$(CH_2)_4$-Hal (to give a pyrrolidino ring), Hal-$(CH_2)_2O(CH_2)_2$Hal (to give a morpholino ring), or Hal-$(CH_2)_2NR^8(CH_2)_2$-Hal (to give a piperazino ring).

According to another process (E), compounds of formula (I) may be prepared from the compounds of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b} and Z are as defined in relation to formula (I), by reaction with a compound of formula (XI)

Hal—X—Y

(XI)

wherein Hal is a halogen atom such as chlorine, bromine or iodine, especially bromine.

The reaction is conveniently effected in the presence of a palladium (0) catalyst, for example, tris(dibenzylidineacetone)dipalladium (0), and a catalytic amount of a co-ordinateing ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or tri-*o*-tolylphosphine, in a suitable solvent such as dioxane or toluene, at an elevated temperature. This reaction is based upon the chemistry described by S. Buchwald in *Tetrahedron*, vol 52, No 21, pp 7525-7546 and *J. Am. Chem. Soc.* 1996, 118, 7215-7216.

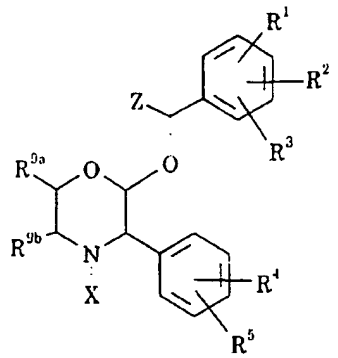
The compounds of formula (II) may be prepared from an intermediate of formula (V) by reaction with an aminocarbonimidate following the procedure of P. J. Garrett, *Tetrahedron* (1993) 49, 165-176.

The compounds of formula (III) may be prepared by the addition of an intermediate of formula (VI)

$$Hal\text{-}CH_2(CH_2)_mOH$$

(VI)

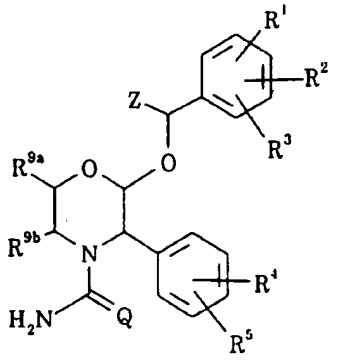
where Hal and m are as previously defined, to a compound of formula (VII)



(VII)

in the presence of a base as previously described in process (D). The resulting alcohol may then be derivatised in a conventional manner using, for example, mesyl or tosyl chloride and triethylamine at an elevated temperature, for example, at reflux.

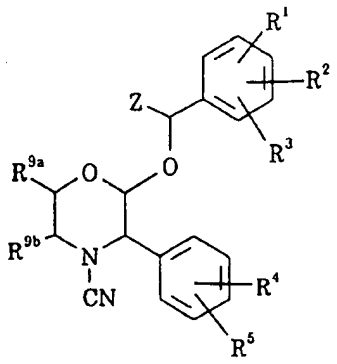
The compounds of formula (IV) may be prepared by conventional methodology. Thus, for example, a compound of formula (IV) where X is a thiazolyl or oxazolyl group, may be prepared from a compound of formula (VIII)



(VIII)

wherein Q is a sulphur or an oxygen atom, by reaction with a compound of the formula Hal-$CH_2C(O)(CH_2)_m$-Hal where each Hal is independently as previously defined, and m is as previously defined, in the presence of a base. The reaction is effected in a suitable solvent such as chloroform, conveniently at a temperature between room temperature and the reflux temperature of the chosen solvent. Suitable bases of use in the reaction include alkali metal carbonates, for example sodium bicarbonate.

Compounds of formula (VIII) where Q is S may be prepared by the reaction of a compound of formula (IX)



(IX)

by reaction with hydrogen sulphide in the presence of a base. The reaction is conveniently effected in a suitable organic solvent such as an alcohol, for example, ethanol. Suitable bases include alkali metal alkoxides, for example, potassium *tert*-butoxide.

Similarly, compounds of formula (VIII) where Q is O may be prepared by the partial hydrolysis of a cyanide of formula (IX) using conventional procedures, for example, using concentrated sulphuric acid; or using formic acid and HCl or HBr; or using acetic acid and BF_3.

Alternatively, compounds of formula (VIII) may be prepared by the reaction of a compound of formula (V) with an isocyanate or isothiocyanate of the formula (X)

$$R^{30}\text{-}N{=}C{=}Q$$

(X)

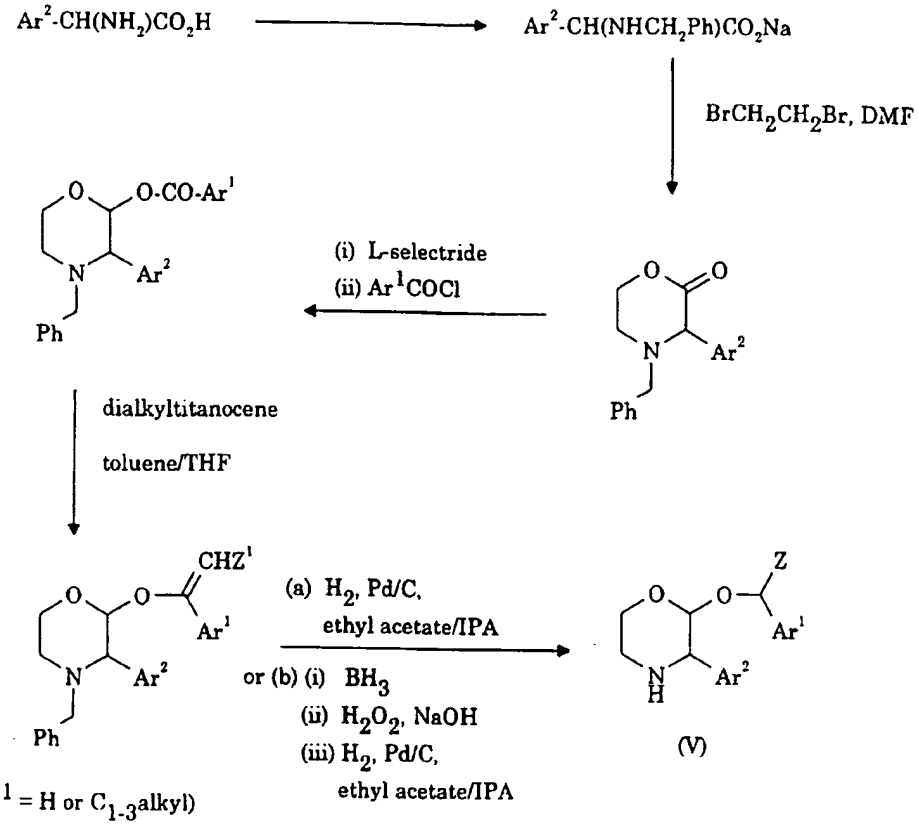
where Q is as previously defined and R^{30} is a suitable amine protecting group, for example, a benzyl group or an alkyl- or aryl-sulphonyl group such as a *p*-toluenesulphonyl group, using conventional methodology.

Compounds of formula (IX) may be prepared by the reaction of a compound of formula (V) with cyanogen bromide in the presence of a base such as an alkali metal carbonate, for example, potassium carbonate.

conveniently in an organic solvent such as *N*,*N*-dimethylformamide, at a temperature between room temperature and 80°C.

Compounds of formula (VII) may be prepared by analogous methods to those described above and those illustrated hereinafter. Such methods will be readily apparent to a person skilled in the art, thus, in a further example, compounds of formula (VII) where X is a tetrazolyl group may be prepared by the reaction of a compound of formula (IX) with a suitable azide such as sodium azide, or ammonium azide (preferably prepared *in situ* from sodium azide and ammonium chloride). The reaction is conveniently effected in a solvent such as *N*,*N*-dimethylformamide at an elevated temperature such as at the reflux temperature of the solvent.

The compounds of formula (V) may be prepared as shown in the following scheme in which Ar^1 represents the R^1, R^2, R^3 substituted phenyl group; Ar^2 represents the R^4, R^5 substituted phenyl group and Ph represents phenyl:



The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the skilled worker has read the disclosure herein.

(i) D.A. Evans *et al.*, *J. Am. Chem. Soc.*, 112, 4011 (1990).

(ii) Yanagisawa, I. *et al.*, *J. Med. Chem.*, 27, 849 (1984).

(iii) Duschinsky, R. *et al.*, *J. Am. Chem. Soc.*, 70, 657 (1948).

(iv) Tebbe F. N. *et al.*, *J. Am. Chem. Soc.*, 100, 3611 (1978).

(v) Petasis, N. A. *et al.*, *J. Am. Chem. Soc.*, 112, 6532 (1990).

(vi) Takai, K. *et al.*, *J. Org. Chem.*, 52, 4412 (1987).

Compounds of formulae (VI), (X) and (XI) are either known compounds or may be prepared by methods which will be readily apparent to one skilled in the art.

The Examples disclosed herein produce predominently the preferred isomers. The unfavoured isomers are also produced on minor components.

If desired they may be isolated and employed to prepare the various stereoisomers in conventional manner, for example chromatography using an appropriate chiral column. However, the skilled worker will appreciate that although the Examples have been optimized to the production of the preferred isomers, variation in solvent, reagents, chromatography etc can be readily employed to yield the other isomers.

L-Selectride is lithium tri-sec-butylborohydride.

Where they are not commercially available, the intermediates above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC_{50} at the NK1 receptor of less than 100nM.

The following Examples illustrate the preparation of compounds according to the present invention:

DESCRIPTION 1

(S)-(4-Fluorophenyl)glycine

Via Chiral Synthesis:

Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09g (33.0mmol) of 4-fluorophenylacetic acid in 100ml of anhydrous ether. The solution was cooled to -10°C and treated with 5.60ml (40.0mmol) of triethylamine followed by 4.30ml (35.0mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at -10°C for 40 minutes, then cooled to -78°C.

An oven-dried, 250ml round bottom flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31g (30.0mmol) of 4-(S)-benzyl-2-oxazolidinone in 40ml of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8ml of 1.6M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was added, via cannula, to the above mixture in the 3-necked flask. The cooling bath was removed from the resulting mixture and the temperature was allowed to rise to 0°C. The reaction was quenched with 100ml of saturated aqueous ammonium chloride solution, transferred to a 1l flask, and the ether and THF were removed *in vacuo*. The concentrated mixture was partitioned between 300ml of methylene chloride and 50ml of water and the layers were separated. The organic layer was washed with 100ml of 2N aqueous hydrochloric acid solution, 300ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 400g of silica gel using 3:2 v/v hexanes/ether as the eluant afforded 8.95g of an oil that slowly solidified on standing. Recrystallisation from 10:1 hexanes/ether afforded 7.89g (83%) of the title compound as a white solid: mp 64-66°C. MS (FAB): m/z 314 (M^++H, 100%), 177 (M-ArCH_2CO+H, 85%). 1H NMR (400MHz, $CDCl_3$) δ 2.76 (1H, dd, J=13.2, 9.2Hz), 3.26 (dd, J=13.2, 3.2Hz), 4.16-4.34 (4H, m), 4.65 (1H, m), 7.02-7.33 (9H, m).

Analysis Calcd. for $C_{18}H_{16}FNO_3$: C, 69.00; H, 5.15; N, 4.47; F, 6.06;
Found: C, 68.86; H, 5.14; N, 4.48; F, 6.08%.

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1l 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0ml of 1M potassium bis(trimethylsilyl)amide solution in toluene and 85ml of THF and was cooled to -78°C. An oven-dried 250ml round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20g (23.0mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Step A) in 40ml of THF. The acyl oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below -70°C. The acyl oxazolidinone flask was rinsed with 15ml of THF and the rinse was added, via cannula, to the reaction mixture and the resulting mixture was stirred at -78°C for 30 minutes. An oven-dried, 250ml round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89g (35.0mmol) of 2,4,6-triisopropylphenylsulfonyl azide in 40ml of THF. The azide solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal temperature of the mixture was maintained below -70°C. After 2 minutes, the reaction was quenched with 6.0ml of glacial acetic acid, the cooling bath was removed and the mixture was stirred at room temperature for 18 hours. The quenched reaction mixture was partitioned between 300ml of ethyl acetate and 300ml of 50% saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 500g of silica gel using 2:1 v/v, then 1:1 v/v

hexanes/methylene chloride as the eluant afforded 5.45g (67%) of the title compound as an oil. IR Spectrum (neat, cm^{-1}): 2104, 1781, 1702. ^1H NMR (400MHz, $CDCl_3$) δ 2.86 (1H, dd, J=13.2, 9.6Hz), 3.40 (1H, dd, J=13.2, 3.2Hz), 4.09-4.19 (2H, m), 4.62-4.68 (1H, m), 6.14 (1H, s), 7.07-7.47 (9H, m).

Analysis Calcd. for $C_{18}H_{15}FN_4O_3$: C 61.01; H, 4.27; N, 15.81; F, 5.36;
Found: C, 60.99; H, 4.19; N, 15.80; F, 5.34%.

Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40g (15.2mmol) of 3-((S)-azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone (from Step B) in 200ml of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28g (30.4mmol) of lithium hydroxide monohydrate was added in one portion and the resulting mixture was stirred cold for 30 minutes. The reaction mixture was partitioned between 100ml of methylene chloride and 100ml of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2 x 100ml of methylene chloride and acidified to pH 2 with 2N aqueous hydrochloric acid solution. The resulting mixture was extracted with 2 x 100ml of ethyl acetate; the extracts were combined, washed with 50ml of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 2.30g (77%) of the title compound as an oil that was used in the following step without further purification. IR Spectrum (neat, cm^{-1}): 2111, 1724. ^1H NMR (400MHz, $CDCl_3$) δ 5.06 (1H, s), 7.08-7.45 (4H, m), 8.75 (1H, br s).

Step D: (S)-(4-Fluorophenyl)glycine

A mixture of 2.30g (11.8mmol) of (S)-azido-(4-fluorophenyl)acetic acid (from Step C), 2.50mg 10% palladium on carbon catalyst and 160ml 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered through Celite and the flask

and filter cake were rinsed well with about 1 litre of 3:1 v/v water/acetic acid. The filtrate was concentrated *in vacuo* to about 50ml of volume. 300ml of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99g (100%) of the title compound. ^{1}H NMR (400MHz, D_2O+ NaOD) δ 3.97 (1H, s), 6.77 (2H, app t, J=8.8Hz), 7.01 (2H, app t, J=5.6Hz).

Via Resolution:

Step A' (4-Fluorophenyl)acetyl chloride

A solution of 150g (0.974mol) of 4-(fluorophenyl)acetic acid and 1ml of N,N-dimethylformamide in 500ml of toluene at 40°C was treated with 20ml of thionyl chloride and heated to 40°C. An additional 61.2ml of thionyl chloride was added dropwise over 1.5 hours. After the addition, the solution was heated at 50°C for 1 hour, the solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 150.4g (89.5%) of the title compound, bp = 68-70°C.

Step B': Methyl 2-bromo-3-(4-fluorophenyl)acetate

A mixture of 150.4g (0.872mol) of 4-(fluorophenyl)acetyl chloride (from Step A') and 174.5g (1.09mol) of bromine was irradiated at 40-50°C with a quartz lamp for 5 hours. The reaction mixture was added dropwise to 400ml of methanol and the solution was stirred for 16 hours. The solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 198.5g (92%) of the title compound, bp = 106-110°C.

Step C': Methyl (±)-(4-fluorophenyl)glycine

A solution of 24.7g (0.1mol) of methyl 2-bromo-2-(4-fluorophenyl)acetate (from Step B') and 2.28g (0.01mol) of benzyl triethylammonium chloride in 25ml of methanol was treated with 6.8g (0.105mol) of sodium azide and the resulting mixture was stirred for 20

hours at room temperature. The reaction mixture was filtered; the filtrate was diluted with 50ml of methanol and hydrogenated in the presence of 0.5g of 10% Pd/C at 50 psi for 1 hour. The solution was filtered and the solvent removed *in vacuo*. The residue was partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The organic phase was washed with water, saturated aqueous sodium chloride solution dried over magnesium sulfate and concentrated *in vacuo* to afford 9.8g of the title compound as an oil.

Step D': Methyl (S)-(4-fluorophenyl)glycinate

A solution of 58.4g of methyl (±) 4-(fluorophenyl)glycinate (from Step C') in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(+)-dibenzoyltartaric acid ((+)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 32.4g of methyl (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 93.2%). The mother liquors were concentrated *in vacuo* and the free base was liberated by partitioning between ethyl acetate and aqueous sodium carbonate solution. A solution of free base, so obtained, in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(-)-dibenzoyltartaric acid ((-)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crysallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 47.0g of methyl (R)-(4-fluorophenyl)glycinate, (-)-DBT salt (ee = 75.8%). Recycling of the mother liquors and addition of (+)-DBT gave a second crop of 7.4g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 96.4%). The two crops of the (S)-amino ester (39.8g) were combined in 200ml of 7:1 v/v ethanol/water, heated for 30 minutes and cooled to room temperature. Addition of ethyl acetate, cooling, and filtration afforded

31.7g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee > 98%). Enantiomeric excess was determined by chiral HPLC (Crownpak CR(+) 5% MeOH in aq $HClO_4$ pH2 1.5ml/min 40°C 200nm).

A mixture of 17.5g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt and 32ml of 5.5N HCl (32ml) was heated at reflux for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 40ml of water. The aqueous solution was washed (3 x 30ml of ethyl acetate) and the layers were separated. The pH of the aqueous layer was adjusted to 7 using ammonium hydroxide and the precipitated solid was filtered to afford 7.4g of the title compound (ee = 98.8%).

DESCRIPTION 2

4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

Step A: N-Benzyl-(S)-(4-fluorophenyl)glycine

A solution of 1.87g (11.05mmol) of (S)-(4-fluorophenyl)-glycine (from Description 1) and 1.12ml (11.1mmol) of benzaldehyde in 11.1ml of 1N aqueous sodium hydroxide solution and 11ml of methanol at 0°C was treated with 165mg (4.4mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12ml (11.1mmol)) and sodium borohydride (165mg (4.4mmol) were added to the reaction mixture and stirring was continued for 1.5hours. The reaction mixture was partitioned between 100ml of ether and 50ml of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2N aqueous hydrochloric acid solution and the solid that had precipitated was filtered, rinsed well with water, then ether, and dried to afford 1.95g of the title compound. ^1H NMR (400MHz, D_2O + NaOD) δ 3.33 (2H, AB q, J=8.4Hz), 3.85 (1H, s), 6.79-7.16 (4H, m).

Step B: 4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

A mixture of 1.95g (7.5mmol) of N-benzyl (S)-(4-fluorophenyl)glycine, 3.90ml (22.5mmol) of N,N-diisopropyl-ethylamine, 6.50ml (75.0mmol) of 1,2-dibromoethane and 40ml of N,N-dimethylformamide was stirred at 100°C for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated *in vacuo*. The residue was partitioned between 250ml of ether and 100ml of 0.5N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100ml of saturated aqueous sodium bicarbonate solution, 3 x 150ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 125g of silica gel using 3:1 v/v hexanes/ether as the eluant afforded 1.58g (74%) of the title compound as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.65 (1H, dt, J=3.2, 12.8Hz), 3.00 (1H, dt, J=12.8, 2.8Hz), 3.16 (1H, d, J=13.6Hz), 3.76 (1H, d J=13.6Hz), 4.24 (1H, s), 4.37 (1H, dt, J=13.2, 3.2Hz), 4.54 (1H, dt, J=2.8, 13.2Hz), 7.07-7.56 (9H, m).

DESCRIPTION 3

4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of 2.67g (10.0mmol) of 4-benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone (Description 2) in 40ml of dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml(20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was

extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. ^{1}H NMR (200MHz, $CDCl_3$) δ 2.50 (1H, dt, J=3.4, 12.0Hz), 2.97 (1H, app d, J=12.0Hz), 2.99 (1H, d, J=13.6Hz), 3.72-3.79 (1H, m), 3.82 (1H, d, J=2.6Hz), 4.00 (1H, d, J=13.6Hz), 4.20 (dt, J=2.4, 11.6Hz), 6.22 (1H, d, J=2.6Hz), 7.22.7.37 (7H, m), 7.57 (2H, app d, J=6.8Hz), 8.07 (1H, s), 8.47 (2H, s). MS (FAB) m/z 528 (M+H, 25%), 270 (100%).

Analysis Calcd. for $C_{26}H_{20}F_7NO_3$: C, 59.21; H, 3.82; N, 2.66; F, 25.21;
Found: C, 59.06; H, 4.05; N, 2.50; F, 25.18%.

DESCRIPTION 4

4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

Step A: Dimethyl titanocene

A solution of 2.49g (10.0mmol) of titanocene dichloride in 50ml of ether in the dark at 0°C was treated with 17.5ml of 1.4M methyllithium solution in ether maintaining the internal temperature below 5°C. The resulting yellow/orange mixture was stirred at room temperature for 30 minutes and the reaction was quenched by slowly adding 25g of ice. The quenched reaction mixture was diluted with 50ml of ether and 25ml of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 2.03g (98%) of the title compound as a light-sensitive solid. The dimethyl titanocene could be stored as a solution in toluene at 0°C for at least 2 weeks without apparent chemical degradation. ^{1}H NMR (200MHz, $CDCl_3$) δ -0.15 (6H, s), 6.06 (10H, s).

Step B: 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of the compound of Description 3 (2.50g, 4.9mmol) and 2.50g (12.0mmol) of dimethyl titanocene (from Step A) in 35ml of 1:1 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. An analytical sample was obtained via recrystallisation from isopropanol: ^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (1H, dt, J=3.6, 12.0Hz), 2.90 (1H, app d, J=12.0Hz), 2.91 (1H, d, J=13.6Hz), 3.62-3.66 (1H, m), 3.72 (1H, d, J=2.6Hz), 3.94 (1H, d, J=13.6Hz), 4.09 (1H, dt, J=2.4, 12.0Hz), 4.75 (1H, d, J=3.2Hz), 4.82 (1H, d, J=3.2Hz), 5.32 (1H, d, J=2.6Hz), 7.09 (2H, t, J=8.8Hz), 7.24-7.33 (5H, m), 7.58-7.62 (2H, m), 7.80 (1H, s), 7.90 (2H, s); MS (FAB) 526 (M+H, 75%), 270 (100%).

Analysis Calcd. for $C_{27}H_{22}F_7NO_2$: C, 61.72; H, 4.22; N, 2.67; F, 25.31;
Found: C, 61.79; H, 4.10; N, 2.65; F, 25.27%.

DESCRIPTION 5

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 4 (4.0g) was dissolved in ethyl acetate (50ml) and isopropanol (16ml). To this solution was added palladium on charcoal (1.5g) and the mixture was hydrogenated at 40 psi for 36h. The catalyst was removed by filtration through Celite and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica using 100% ethyl acetate and then 1-10% methanol in ethyl acetate. This afforded isomer A 500mg (15%) and isomer B 2.6g (80%) as clear oils - isomer B crystallised on standing. For the title compound: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.8MHz), 1.80 (1H, br s), 3.13 (1H, dd, J=3.2, 12.4Hz), 3.23 (1H, dt, J=3.6, 12.4Hz), 3.63 (1H, dd, J=2.4, 11.2Hz),

4.01 (1H, d, J=2.4Hz), 4.13 (1H, dt, J=3.2, 12.0Hz), 4.42 (1H, d, J=2.4Hz), 4.19 (1H, q, J=6.8Hz), 7.04-7.09 (2H, m), 7.27-7.40 (4H, m), 7.73 (1H, s); MS (FAB) 438 (M+H, 75%), 180 (100%).

HCl salt formation. To a solution of the free base (0.77g) in diethyl ether (10ml) was added 1M-HCl in methanol (1.75ml). The solution was evaporated to dryness and on addition of diethyl ether crystals formed. The solution was filtered and the residue washed with diethyl ether to give the title compound hydrochloride salt mp 248-250°C.

Analysis Calcd. for $C_{20}H_{18}F_7NO_2$.HCl: C, 50.70; H, 4.04; N, 2.96; Cl, 7.48;
Found: C, 50.46; H, 3.85; N, 3.01; Cl, 7.31%.

DESCRIPTION 6

4-Benzyl-3-(S)-phenyl-2-morpholinone

Step A: N-Benzyl-(S)-phenylglycine

A solution of 1.51g (10.0mmol) of (S)-phenylglycine in 5ml of 2N aqueous sodium hydroxide solution was treated with 1.0ml (10.0mmol) of benzaldehyde and stirred at room temperature for 20 minutes. The solution was diluted with 5ml of methanol, cooled to 0°C, and carefully treated with 200mg (5.3mmol) of sodium borohydride. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with 20ml of water and extracted with 2 x 25ml of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid to pH 6 and the solid that precipitated was filtered, washed with 50ml of water, 50ml of 1:1 v/v methanol/ethyl ether and 50ml of ether, and dried to afford 1.83g (76%) of product. mp 230-232°C.

Analysis Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81;
Found: C, 74.17; H, 6.19; N, 5.86%.

Step B: 4-Benzyl-3-(S)-phenyl-2-morpholinone

A mixture of 4.00g (16.6mmol) of N-benzyl-(S)-phenylglycine (from Step A) 5.00g (36.0mmol) of potassium carbonate, 10.0ml of 1,2-dibromoethane and 25ml of N,N-dimethylformamide was stirred at 100°C for 20 hours. The mixture was cooled and partitioned between 200ml of ethyl ether and 100ml of water. The layers were separated and the organic layer was washed with 3 x 50ml of water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on 125g of silica gel eluting with 9:1 v/v, then 4:1 hexanes/ethyl ether to afford 2.41g (54%) of the product as a solid, mp 98-100°C. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.54-2.68 (1H, m), 2.96 (1H, dt, J=12.8, 2.8Hz), 3.14 (1H, d, J=13.3Hz), 3.75 (1H, d, J=13.3Hz), 4.23 (1H, s), 4.29-4.37 (1H, m), 4.53 (dt, J=3.2, 11.0Hz), 7.20-7.56 (10H, m). MS (FAB): m/z 268 (M+H; 100%).

DESCRIPTION 7

4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-phenylmorpholine

A solution of 2.67g (10.0mmol) of the compound of Description 6 in 40ml of dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml (20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of

silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. ^{1}H NMR (200MHz, $CDCl_3$) δ 2.50 (1H, dt, J=3.4, 12.0Hz), 2.97 (1H, app d, J= 12.0Hz), 2.99 (1H, d, J=13.6Hz), 3.72-3.79 (1H, m), 3.82 (1H, d, J=2.6Hz), 4.00 (1H, d, J=13.6Hz), 4.20 (dt, J=2.4, 11.6Hz), 6.22 (1H, d, J=2.6Hz), 7.22-7.37 (7H, m), 7.57 (2H, app d, J=6.8Hz), 8.07 (1H, s), 8.47 (2H, s).

Analysis Calcd. for $C_{26}H_{21}F_6NO_3$: C, 61.29; H, 4.16; N, 2.75; F, 22.38;
Found: C, 61.18; H, 4.14; N, 2.70; F, 22.13%.

DESCRIPTION 8

4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-phenylmorpholine

A solution of 2.50g (4.9mmol) of the compound of Description 7 and 2.50g (12.0mmol) of dimethyl titanocene (Description 4a), in 35ml of 1:1 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (1H, dt, J=3.6, 12.0Hz), 2.89 (app d, J=11.6Hz), 2.92 (1H, d, J=13.6Hz), 3.61-3.66 (1H, m), 3.73 (1H, d, J=2.8Hz), 4.00 (1H, d, J=13.6Hz), 4.09 (1H, dt, J=2.4, 11.6Hz), 4.75 (1H, d, J=2.8Hz), 4.79 (1H, d, J=2.8Hz), 5.36 (1H, d, J=2.4Hz), 7.23-7.41 (7H, m), 7.63 (1H, app d, J=7.2Hz), 7.79 (1H, s), 7.91 (2H, s). MS (FAB) m/z 508 (M+1, 25%).

Analysis Calcd. for $C_{27}H_{23}F_6NO_2$: C, 63.90; H, 4.57; N, 2.76; F, 22.46;
Found: C, 63.71; H, 4.53; N, 2.68; F, 22.66%.

DESCRIPTION 9

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenylmorpholine

A mixture of the compound of Description 8 (1.5g) and 10% palladium on carbon catalyst (750mg) in a mixture of isopropanol/ethyl acetate (25ml, 3:2 v/v) was stirred under an atmosphere of hydrogen for 48h. The catalyst was removed by filtration through celite and the reaction flask and filter pad were rinsed with ethyl acetate (500ml). The filtrate was concentrated *in vacuo*, flash chromatography afforded epimer A (106mg) and epimer B (899mg) as clear oils. The title compound, epimer B had the following analysis:

^{1}H NMR ($CDCl_3$, 400MHz) δ 1.46 (3H, d, J=6.8Hz), 1.92 (1H, br s), 3.13 (1H, dd, J=3.0, 12.6Hz), 3.24 (1H, dt, J=3.6, 12.6Hz), 3.62 (1H, dd, J=3.6, 11.2Hz), 4.04 (1H, d, J=2.4Hz), 4.14 (1H, dt, J=3.0, 11.2Hz), 4.48 (1H, d, J=2.4Hz), 4.90 (1H, q, J=6.8Hz), 7.21-7.32 (7H, m), 7.64 (1H, s). MS (Cl^+) m/z 420 (M^++1, 20%), 178 (100%).

Analysis Calcd. for $C_{20}H_{19}F_6NO_2$: C, 57.28; H, 4.57; N, 3.34; F, 27.18;
Found: C, 57.41; H, 4.61; N, 3.29; F, 27.23%.

DESCRIPTION 10

(*N*-Phenylcyanocarbonimidate 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-phenylmorpholine

The title compound was synthesised following the procedure of Garrett P.J. *Tetrahedron* (1993) 49, 165-176. The product of Description 9 (2.0g, 0.45mmol) was dissolved in 2-propanol (40ml), diphenyl aminocarbonimidate (2.18g, 0.9mmol) was added and the reaction heated to 80°C for 16h. The solvent was then removed and the product purified on silica eluting with hexane-ethyl acetate mixtures to give the title compound as an oil (1.2g).

DESCRIPTION 11

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-cyano-3-(S)-(4-fluorophenyl)morpholine

The product of Description 5 (2.0g, 4.57mmol) was dissolved in dimethylformamide (20ml), cyanogen bromide (727mg, 6.86mmol) was added followed by potassium carbonate (1.89g, 13.7mmol) and the reaction heated to 60°C for 16h. The reaction was then poured into ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Purification on silica eluting with hexane-ethyl acetate mixtures gave the title compound (2.01g). ^1H NMR (250MHz, $CDCl_3$) δ 1.51 (3H, d, J=6.6Hz), 3.42-3.60 (2H, m), 3.63-3.71 (1H, m), 4.22 (1H, d, J=2.6Hz), 4.25-4.34 (1H, m), 4.37 (1H, d, J=2.6Hz), 4.88 (1H, q, J=6.6Hz), 7.09 (2H, t, J=8.6Hz), 7.22 (2H, s), 7.40-7.46 (2H, m), 7.67 (1H, s).

DESCRIPTION 12

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-tetrazol-5-yl-morpholine

The product of Description 11 (280mg, 0.6mmol) was dissolved in dimethylformamide (15ml), sodium azide (78mg, 1.2mmol) was added followed by ammonium chloride (64mg, 1.2mmol) and the reaction heated to 160°C for 16h. The reaction was then poured into ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Purification on silica eluting with hexane-ethyl acetate mixtures gave the title compound. ^1H NMR (250MHz, $CDCl_3$) δ 1.35 (3H, d, J=6.6Hz), 3.44-3.58 (1H, m), 3.70-3.80 (2H, m), 4.60 (1H, d, J=3.3Hz), 4.78 (1H, d, J=3.3Hz), 4.95 (1H, q, J=6.5Hz), 6.82-6.94 (2H, m), 7.39 (2H, s), 7.40-7.52 (2H, m), 7.67 (1H, s).

DESCRIPTION 13

2-(R)-1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2-hydroxyethyl-2*H*-tetrazol-5-yl)morpholine

The product of Description 12 (610mg, 1.21mmol) was dissolved in diemthylformamide (5ml). Potassium carbonate (757mg, 5.47mmol) was added followed by 2-bromoethanol (256µl, 3.62mmol) and the reaction

heated to 60°C for 16h. The reaction was then poured into ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Purification on silica eluting with hexane-ethyl acetate gave the title compound (335mg). ^1H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 2.26 (1H, br t), 3.62-3.66 (2H, m), 3.79-3.89 (1H, m), 3.95-4.01 (2H, m), 4.22-4.29 (1H, m), 4.45-4.52 (2H, m), 4.68 (1H, d, J=3.3Hz), 4.85 (1H, d, J=3.3Hz), 5.05 (1H, q, J=6.5Hz), 6.99 (2H, t, J=8.7Hz), 7.53-7.59 (4H, m), 7.76 (1H, s).

DESCRIPTION 14

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2-*p*-toluenesulphonylethyl-2*H*-tetrazol-5-yl)morpholine

The product of Description 13 (335mg, 0.61mmol) was dissolved in dichloromethane (10ml), tosyl chloride (232mg, 1.22mmol) was added followed by triethylamine (171µl, 2.34mmol) and the reaction heated to reflux for 16h. The solvent was then removed and the residue redissolved in ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Purification on silica eluting with hexane-ethyl acetate gave the title compound (0.25g). ^1H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 2.41 (3H, s), 3.46-3.63 (2H, m), 3.78-3.87 (1H, dt, J=3.9 and 10.2Hz), 4.19-4.24 (1H, dt, J=3.3 and 11.3Hz), 4.41 (2H, t, J=5.2Hz), 4.58 (2H, t, J=5.7Hz), 4.70 (1H, d, J=3.3Hz), 4.89 (1H, d, J=3.34Hz), 5.05-5.08 (1H, q, J=6.5Hz), 6.97 (2H, t, J=8.7Hz), 7.27 (2H, d, J=7.87Hz), 7.55-7.61 (4H, m), 7.67 (2H, d, J=6.6Hz), 7.77 (1H, s).

EXAMPLE 1

4-(5-Amino-1,2,4-triazol-3-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenylmorpholine

The product of Description 10 (1.80g, 1.85mmol) was dissolved in 2-propanol (30ml), hydrazine (180µl, 3.7mmol) was added and the reaction heated to 80°C for 16h. The solvent was then removed and the residue

purified on silica eluting with dichloromethane-methanol mixtures to give the title compound (0.4g). ^{1}H NMR (250MHz, $CDCl_3$) δ 1.31 (3H, d, J=6.5Hz), 3.22-3.40 (2H, m), 3.71-3.74 (1H, dt, J=7.2 and 3.7Hz), 3.94-4.00 (1H, m), 4.50 (3H, m), 4.90 (1H, q, J=6.5Hz), 4.96-5.04 (2H, m), 6.90 (2H, t, J=17.5Hz), 7.50-7.64 (5H, m). M/S M^+ 502.

EXAMPLE 2

2-(R)-1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(2-*N,N*-dimethylaminoethyl-2*H*-tetrazol-5-yl)-3-(S)-(4-fluorophenyl)morpholine

The product of Description 14 (250mg, 0.355mmol) was dissolved in dimethylformamide (10ml), dimethylamine (2ml) was added and the reaction heated in a sealed tube at 60°C for 16h. The reaction was then poured into ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. Purification on silica eluting with dichloromethane-methanol mixtures gave the title compound (0.13g). ^{1}H NMR (250MHz, $CDCl_3$) δ 1.37 (3H, d, J=6.6Hz), 2.14 (6H, s), 2.67-2.71 (2H, dt, J=1.6 and 6.65Hz), 3.43-3.59 (2H, m), 3.72-3.80 (1H, dt, J=3.7 and 9.9Hz), 4.12-4.19 (1H, m), 4.61 (1H, d, J=3.3Hz), 4.82 (1H, d, J=3.3Hz), 4.99 (1H, q, J=6.5Hz), 6.86-6.94 (2H, m), 7.50-7.55 (4H, m), 7.70 (1H, s,). M/S M^+ 577.

EXAMPLE 3

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-*N,N*-dimethylaminomethyl)thiazol-2-yl)-3-(S)-(4-fluorophenyl)morpholine

a) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-aminothiocarbonyl-3-(S)-(4-fluorophenyl)morpholine

Through a solution of the product of Description 11 (1.07g) in ethanol (25ml) was bubbled hydrogen sulphide for 10 minutes. Potassium *tert*-butoxide (0.05g) was added and addition of hydrogen sulphide was continued for 16 hours whilst the solution was heated at 50°C. Glacial

acetic acid (0.1ml) was added and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting successively with 20% and 50% ethyl acetate in petroleum ether (bp 60-80°C) to give the title compound (0.57g). ^{1}H NMR($CDCl_3$, 250MHz) δ 7.68 (1H,s), 7.31-7.72 (4H,m), 7.02 (2H,t, J=8.6Hz), 5.51 (2H,br. s), 5.21 (1h,d, J=4.1Hz), 4.95-4.90 (2H,m), 4.6 (1H,d, J=4.2Hz), 4.0-3.8 (3H,m), 1.38 (3H,d, J=6.6Hz).

b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-chloromethyl)thiazol-2-yl)-3-(S)-(4-fluorophenyl)morpholine

To a solution of the product of step (a) (0.534g) in chloroform (20ml) was added sodium bicarbonate (0.39g) and 1,3-dichloroacetone (0.165g). The solution was stirred at 50°C for 3 hours followed by heating at reflux in a Dean and Stark apparatus containing 3Å molecular sieves for 2 hours. The cooled solution was evaporated and the residue purified on silica gel eluting with 15% ethyl acetate in petroleum ether (bp 60-80°C) to give the title compound (0.487g). ^{1}H NMR($CDCl_3$, 250MHz) δ 7.77 (1H,s), 7.61-7.54 (4H,m), 7.02 (2H,td, J=8.6Hz and 2.1Hz), 6.48 (1H,s), 5.04 (1H,q, J=6.6Hz), 4.87 (1H,d, J=3.4Hz), 4.66 (1H,d, J=3.46Hz), 4.44 (2H,d, J=0.64Hz), 4.19 (2H,dt, J=11.3Hz and 3.32Hz), 3.92-3.62 (3H,m), 1.46 (3H,d, J=6.6Hz).

c) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-*N*,*N*-dimethylaminomethyl)thiazol-2-yl)-3-(S)-(4-fluorophenyl)morpholine

Through a solution of the product of step (b) (0.109g) in ethanol (5ml) was passed diethylamine gas until saturated. The flask was sealed for 16 hours whereupon the solvent was removed *in vacuo* and the residue purified on silica gel eluting with 20% methanol in ethyl acetate. The residue after evaporation (0.063g) was dissolved in 1M HCl in methanol (1ml), evaporated to dryness and washed with hexane. After drying *in vacuo* this gave the title compound as a foam. ^{1}H NMR($CDCl_3$, 360MHz) δ 7.76 (1H,s), 7.5 (4H,m), 7.01 (2H,t, J=8.7Hz), 6.8 (1H,s), 5.0 (1H,q,

J=6.5Hz), 4.85 (1H,d, J=3.5Hz), 4.65 (1H,d, J=3.5Hz), 4.22 (1H,dt, J=11.0Hz), 3.91-3.79 (4H,m), 3.6 (1H,ddd), 2.62 (6H,s), 1.44 (3H,d, J=6.6Hz). MS m/z (CI^+) 578 (M+H).

EXAMPLE 4

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(2-amino-5-thiazolyl)-3-(S)-(4-fluorophenyl)morpholine

To a degassed solution of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)-phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine (0.2g), 2-amino-5-bromothiazole (0.14g), sodium *tert*-butoxide (0.0105g) and tri-*o*-tolylphosphine (0.007g) in dioxane (4ml) was added tris(dibenzylideneacetone)dipalladium (0) (0.02g). The solution was degassed and then heated at 80°C for 24h under an atmosphere of nitrogen. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and after evaporation of the solvent the residue was chromatographed on silica (eluting with gradient of 2% -4% methanol/ammonia (100:3) in dichloromethane) to give the title compound. ^1H NMR (360MHz, $CDCl_3$) δ 3.11 (1H, td, J=11.7Hz, 3.5Hz), 3.19 (1H, bd J=11.4Hz), 3.61 (1H, dd, J=12.2Hz and 3.3Hz), 3.67-3.81 (3H, m), 4.47 (1H, d, J=2.8Hz), 4.54 (1H. td, J=11.7Hz and 2.8Hz), 4.80 (2H, bs), 4.92 (1H, dd, J=7.8Hz and 3.1Hz), 6.97 (2H, t, J=8.7Hz), 7.09 (1H, s), 7.14 (2H, s), 4.91 (1H, dd, J=7.8Hz and 3.1Hz), 7.67 (1H, s); m/z EI^+ 552(M+H).

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 5A Tablets containing 1-25mg of compound

	Amount mg		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0

Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium stearate	0.5	0.5	0.5

EXAMPLE 5B Tablets containing 26-100mg of compound

	Amount mg		
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium stearate	0.5	0.5	0.5

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 6 Parenteral injection

	Amount mg
Compound of formula (I)	1 to 100mg
Citric acid monohydrate	0.75mg
Sodium phosphate	4.5mg
Sodium chloride	9mg
Water for injection	to 10ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 7 Topical formulation

	Amount mg
Compound of formula (I)	1-10g
Emulsifying wax	30g
Liquid paraffin	20g
White soft paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

EXAMPLE 8A - (Surface-Active Agent) Injection Formulation

Compound of formula (I)	up to 10mg/kg
Tween 80™	up to 2.5%

[in 5% aqueous mannitol (isotonic)]

The compound of formula (I) is dissolved directly in a solution of the commercially available Tween 80™ (polyoxyethylenesorbitan monooleate) and 5% aqueous mannitol (isotonic).

EXAMPLE 8B - (Emulsion) Injection Formulation

Compound of formula (I)	up to 30mg/ml
Intralipid™ (10-20%)	

The compound of formula (I) is dissolved directly in the commercially available Intralipid™ (10 or 20%) to form an emulsion.

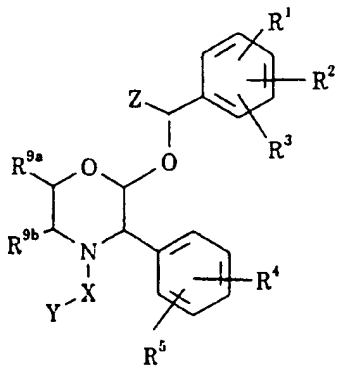
EXAMPLE 8C - Alternative (Emulsion) Injectable Formulation

	Amount
Compound of formula (I)	0.1 - 10mg
Soybean oil	100mg
Egg phospholipid	6mg
Glycerol	22mg
Water for injection	to 1ml

All materials are sterilized and pyrogen free. The compound of formula (I) is dissolved in soybean oil. An emulsion is then formed by mixing this solution with the egg phospholipid, glycerol and water. The emulsion is then sealed in sterile vials.

CLAIMS:

1. A compound of the formula (I):



(I)

wherein

X is a 5- or 6-membered C-linked heteroaromatic ring containing 1 to 4 nitrogen atoms and optionally containing in the ring one oxygen or sulphur atom;

Y is a group of the formula $-(CH_2)_nNR^6R^7$, or a methylene- or ethylene-linked imidazolyl group;

Z is hydrogen or C_{1-4}alkyl optionally substituted by a hydroxy group;

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^3 is hydrogen, halogen or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or

C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxy;

R^7 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxy or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring of 4 to 7 ring atoms, which ring may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR^8, S(O) or $S(O)_2$ and which ring may be optionally substituted by one or two groups selected from hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, oxo, COR^a or CO_2R^a where R^a is as previously defined;

or R^6 and R^7 together with the nitrogen atom to which they are attached, form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

R^8 is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring; and

n is zero, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound a claimed in Claim 1 wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

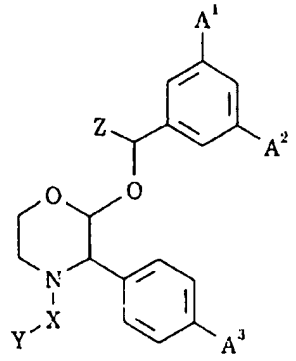
4. A compound as claimed in any one of Claims 1 to 3 wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

5. A compound as claimed in any one of Claims 1 to 4 wherein R^4 is hydrogen.

6. A compound as claimed in any one of Claims 1 to 5 wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

7. A compound as claimed in any one of Claims 1 to 6 wherein R^{9a} and R^{9b} are each independently hydrogen or methyl.

8. A compound of the formula (Ia):



(Ia)

wherein

A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

X is a 5- or 6-membered C-linked heteroaromatic ring containing 1 to 4 nitrogen atoms and optionally containing in the ring one oxygen or sulphur atom;

Y is a group of the formula $-(CH_2)_nNR^6R^7$, or a methylene- or ethylene-linked imidazolyl group;

Z is hydrogen or C_{1-4}alkyl optionally substituted by a hydroxy group;

or a pharmaceutically acceptable salt thereof.

9. A compound as claimed in any one of Claims 1 to 8 wherein X is selected from imidazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, thiadiazolyl and oxadiazolyl.

10. A compound as claimed in any one of Claims 1 to 9 wherein Y is a group of the formula $-(CH_2)_nNR^6R^7$.

11. A compound as claimed in any one of Claims 1 to 10 wherein Z is a C_{1-2}alkyl group optionally substituted by a hydroxy group.

12. A compound selected from:

4-(5-amino-1,2,4-triazol-3-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-N,N-dimethylaminoethyl-2H-tetrazol-5-yl)-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-dimethylaminomethyl)thiazol-2-yl)-3-(S)-(4-fluorophenyl)morpholine;

or a pharmaceutically acceptable salt thereof.

13. A compound as claimed in any preceding claim for use in therapy.

14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 12 in association with a pharmaceutically acceptable carrier or excipient.

15. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1.

16. A method according to claim 15 for the treatment or prevention of pain or inflammation.

17. A method according to claim 15 for the treatment or prevention of migraine.

18. A method according to claim 15 for the treatment or prevention of emesis.

19. A method according to claim 15 for the treatment or prevention of postherpetic neuralgia.

20. The use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

21. The use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

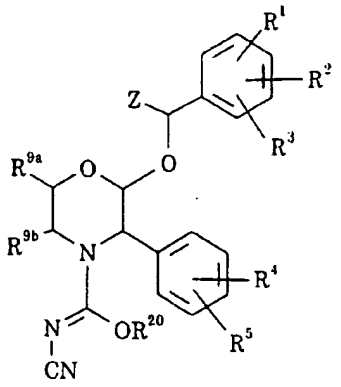
22. The use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of migraine.

23. The use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of emesis.

24. The use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.

25. A process for the preparation of a compound as claimed in Claim 1 which comprises:

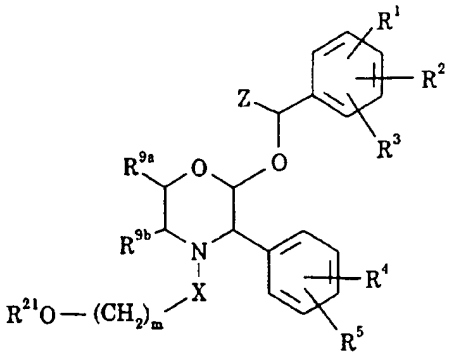
(A), reaction of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b} and Z are as defined in Claim 1 and R^{20} is phenyl or C_{1-6}alkyl, with hydrazine; or

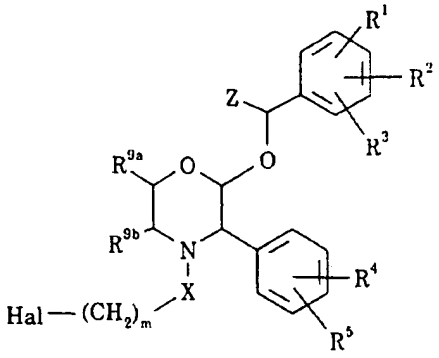
(B), reaction of a compound of formula (III)



(III)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, X and Z are as defined in Claim 1, R^{21} is a leaving group, and m is 1 or 2, with an amine of the formula HNR^6R^7 or imidazole; or

(C), reaction of a compound of formula (IV)

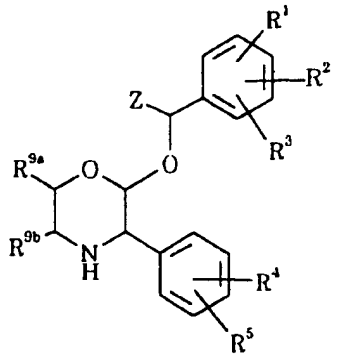


(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, X and Z are as defined Claim 1 and Hal is a halogen atom and m is 1 or 2, with an amine of the formula HNR^6R^7 or imidazole; or

(D), interconversion of a compound of formula (I) in which the heteroaromatic ring represented by X is substituted by a group of the formula $-(CH_2)_nNH_2$, by reaction with alkyl halides of the formula R^6-Hal and R^7-Hal, or a suitable dihalide designed to form a saturated heterocyclic ring, wherein R^6 and R^7 are as defined in Claim 1, and Hal is as previously defined, in the presence of a base;

(E), reaction of a compound of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b} and Z are as defined in Claim 1, with a compound of formula (XI)

Hal—X—Y

(XI)

wherein Hal is a halogen atom;

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt or prodrug thereof.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 96/02766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/04 C07D417/04 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 18124 A (MERCK SHARP & DOHME LTD.) 6 July 1995 see claims ---	1-25
A	WO 95 23798 A (MERCK & CO. INC.) 8 September 1995 see claims ---	1-25
A	WO 95 16679 A (MERCK & CO. INC.) 22 June 1995 see claims ---	1-25
A	EP 0 577 394 A (MERCK & CO. INC.) 5 January 1994 cited in the application see claims --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 1997	10.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 96/02766

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 95 30674 A (MERCK SHARP & DOHME LTD.) 16 November 1995 see claims	1-25
P,A	WO 96 29328 A (MERCK SHARP & DOHME LTD.) 26 September 1996 see claims	1-25

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 96/02766

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 96/02766

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9518124	06-07-95	AU-A-	1322395	17-07-95
		CA-A-	2178219	06-07-95
		EP-A-	0737192	16-10-96
		NO-A-	962749	28-08-96
		PL-A-	315182	14-10-96
		ZA-A-	9410317	10-10-95
		FI-A-	951762	13-10-95
WO-A-9523798	08-09-95	AU-A-	1975095	18-09-95
		CA-A-	2183250	08-09-95
		EP-A-	0748320	18-12-96
		FI-A-	963450	03-09-96
		NO-A-	963675	04-11-96
		US-A-	5512570	30-04-96
		ZA-A-	9501780	15-11-95
WO-A-9516679	22-06-95	AU-A-	1437595	03-07-95
		CA-A-	2178949	22-06-95
		EP-A-	0734381	02-10-96
		FI-A-	962489	13-08-96
		NO-A-	962523	16-08-96
		PL-A-	315153	14-10-96
		ZA-A-	9410008	15-07-96
EP-A-577394	05-01-94	AU-A-	4156893	06-01-94
		AU-A-	4656193	24-01-94
		BG-A-	99274	30-04-96
		CA-A-	2099233	30-12-93
		CN-A-	1087902	15-06-94
		CZ-A-	9403330	13-09-95
		FI-A-	946133	28-12-94
		HR-A-	931003	28-02-95
		HU-A-	71809	28-02-96
		JP-A-	6172178	21-06-94
		NO-A-	945064	28-02-95
		NZ-A-	254476	25-09-96
		SI-A-	9300346	31-12-93
		SK-A-	160094	11-07-95
		WO-A-	9400440	06-01-94
		AU-A-	4160893	06-01-94

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 96/02766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-577394		ZA-A- 9304624	20-06-94
WO-A-9530674	16-11-95	AU-A- 2349395	29-11-95
WO-A-9629328	26-09-96	AU-A- 5009896	08-10-96